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European Journal of Pharmaceutics and Biopharmaceutics 50 (2000) 345–351

European Journal of Pharmaceutics and Biopharmaceutics

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Research report

A new oral erosion controlled drug delivery system with a late burst in the release profile ☆

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Received 6 June 2000; accepted in revised form 11 August 2000

Abstract

A new oral erosion controlled drug delivery system on the basis of polyvinyl alcohols with a late burst in the release profile is developed. This late burst occurs after addition of sparingly soluble substances, either excipients like carboxylic acids and neutral cellulose or drugs like theophylline and theobromine. The onset time between 4 and 12 h and the extent of the burst between 20 and 60% are well reproducible and depend on the type of the used additive and the particle size of the basic polymer. For dissociating additives like glutamic acid, the pH within the swelling and eroding hydrocolloid tablet is decisive, differing from the pH of the dissolution medium and controlling the release process. Only polyvinyl alcohols with a ratio of viscosity number to degree of hydrolysis in the range from 2.3 to 3 exhibit acceleration of release in the final phase. As mechanism of the burst, enforced erosion of the gel layer, surrounding the tablet core, could be identified.

Keywords: Burst effect; Drug delivery system; Hydrocolloid tablets; Modified drug release; pH-dependent solubility; Polyvinyl alcohol

1. Introduction

Hydrocolloid embeddings as drug delivery systems for extended release are often described in the literature [1–3]. The mechanism of release from such hydrocolloid dosage forms includes diffusion, abnormal transport and/or erosion. The main drawback of the diffusion controlled systems is the decreasing amount of released drug with time. Eroding systems with zero-order release kinetics can be produced using a mixture of ionic and non-ionic cellulose ethers in specific combinations [4,5]. Möckel and Lippold [6], obtained linear dissolution profiles also with polyvinyl alcohols as hydrocolloid carrier. However, for biopharmaceutical or chronopharmacological reasons, it may be reasonable to accelerate the drug delivery at the end of the release process.

Shah [7], observed a bimodal release in the case of some hydroxypropyl methylcellulose types and explained the increasing release rate in the final phase of release with the beginning disintegration of the tablet due to complete hydration of the hydrocolloid. Surprisingly, the sigmoid release was only shown by some of the different hydroxypropyl methylcellulose types, all purchased from the same manufacturer. Since the described bimodal characteristic only occurs at stirring rates of 300 rev./min, such a system seems not to be successfully applicable in vivo. Nakano and Ogata [8], described an increase of drug release with sodium alginate as the basic polymer. However, the described results could not be reproduced within the framework of screening studies. Thus, up to now rather complex systems only, such as coat core tablets [9] or laminated matrices [10] are available to realize accelerating release profiles.

It is the aim of this work to develop an oral controlled release dosage form on the basis of a hydrocolloid with an uniform structure and a reproducible burst in the dissolution profile. Starting point of this development is the pH-dependent solubility of acidic additives, dissolving better with increasing pH-value in the gastrointestinal tract [11].

Thus, it should be possible to design a hydrocolloid dosage form which shows faster erosion and drug release rates, respectively, while the release medium exceeds a specific pH-value.

As additives different carboxylic acids are used with low solubility in an acid environment and high solubility in a neutral or slightly alkaline medium. Additionally, glutamic acid and neutral insoluble substances serve as additives. Different polyvinyl alcohols are used as embedding materi-

☆ Part of the PhD. project of O.L. Freichel.

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0939-6411/00/$ - see front matter
PII: S0939-6411(00)00120-X

als. Model drugs are pentoxifylline, theophylline and theobromine.

2. Materials and methods

2.1. Materials

The following polyvinyl alcohols, Polyviol® W25/100, Polyviol® W25/140, Polyviol® W25/190, Polyviol® M05/20, Polyviol® WX 28/20, Polyviol® W45/450, Polyviol® M13/140, Polyviol® M05/140 were purchased from Wacker Chemie GmbH (München, Germany). Mowiol® 10/98 and Mowiol® 20/98 were from Hoechst AG (Frankfurt, Germany). PVA 100 000 was from Merck KaAG (Darmstadt, Germany), in most cases a particle size of 100–140 μm is used. Glutamic acid and adipic acid were provided by Fluka Chemie AG (Buchs, Switzerland). Sebacic acid, succinic acid, azelainic acid and lauric acid were purchased from Merck & Schuchardt (Hohenbrunn, Germany). Eudragit RL-PO® (particle size 45–100 μm), a methacrylic acid copolymer, was provided from Röhm GmbH (Darmstadt, Germany). Microcrystalline cellulose, Avicel® PH 101 was purchased from FMC Corporation (Philadelphia, PA). Ethyl cellulose, Ethocel® STD 10 IND (particle size 100–140 μm) was from Dow Chemical Company (Midland, USA). Methylene blue was from Merck KaAG. Pentoxifylline was a gift from Hoechst AG (Frankfurt, Germany). Theophylline and Theobromine were obtained from Caesar & Loretz GmbH (Hilden, Germany).

2.2. Methods

2.2.1. Determination of pH-dependent solubility of glutamic acid

Saturated solutions of glutamic acid in different buffers with pH-values between pH 1 and 6 are shaken automatically for 24 h at a temperature of 20 ± 1°C. The solid content of filtered specimens of 10 ml is determined gravimetrically after drying to constant weight at 100°C. After subtraction of the buffer salts the dissolved amount of glutamic acid results.

The pKa-values of the glutamic and sebacic acid are determined using the difference-titration method described by Parke and Davis [12].

2.2.2. Dissolution studies

Eight hundred milligram tablets are prepared by direct compression of the powdered components using a hand-hydraulic KBr press (Perkin–Elmer), at a compression force of 20 kN. All tablets are initially approximately 4.5 mm thick and have a diameter of 13 mm.

The paddle apparatus Ph. Eur. 1997 is used with 1000 ml of different media at a temperature of 37 ± 0.5°C for the dissolution studies. The stirring speed is 100 rev./min to prevent sticking of the tablets to the vessel. Different media for the individual dissolution studies are used: 0.1 M HCl (pH 1.1), and phosphate buffers for pH-values between 2.3 and 7.8. The ionic strength is adjusted to approximately 0.1. The dissolution studies are carried out either at a defined pH-value during the entire dissolution or a pH-gradient is implemented by transferring the tablets after predetermined time periods in other media. In all cases the pH of the dissolution medium does not change during the release process. All experiments are repeated at least three times. The concentration of the drugs in the medium is determined by continuous UV-absorption measurements in a flow-through cell.

2.2.3. Determination of extent of erosion parallel to drug release

The dissolution studies are stopped at specific times to investigate the mechanism of release progression more closely. The tablets are then taken out of the dissolution apparatus and their weights are determined after drying under vacuum for 72 h at ambient temperature over phosphorus pent oxide. The percentage of the tablet erosion is calculated in relation to the initial dry weight of the tablets, according to Eq. (1):

$$\text{Erosion}(\%) = \left(1 - \frac{\text{dry weight}(t)}{\text{initial dry weight}}\right) \times 100\% \qquad (1)$$

The percentage of tablet erosion is characterized at three or four different times.

2.2.4. Dissolution studies with a perspex mount

For a better visual observation of the dissolution process and for the clarification of the mechanism of release progression, tablets containing 0.25% of methylene blue as erosion marker are prepared.

The resulting tablets are fixed between two perspex disks (6 × 6 cm) with the aid of four leaf screws. Only the body surface of the tablet is accessible for the dissolution medium. The entire perspex mount is then transferred in the paddle apparatus Ph. Eur. with a paddle distance of 6 cm from the bottom of the vessel. The mount is taken out at defined times and the resulting state of the tablet is imaged with a flat-bed scanner.

2.3. Properties of the carboxylic acids, glutamic acid and the model drugs

Table 1 gives information about the characteristics of the carboxylic acids and of glutamic acid. pKa-values of all used carboxylic acids are in the range between 4.18 and 5.63. The solubilities of the acids in water decrease with increasing chain length. The lauric acid as mono carboxylic acid shows an extremely low solubility in water. All carboxylic acids show increasing solubilities with increasing pH-value (pH > pKa −2) due to increasing dissociation. Glutamic acid, as a monoamino dicarboxylic acid, behaves differently (Fig. 1), due to the existence of three pKa and the formation of the less soluble zwitterion.

Table 1
Properties of the organic acids

Acid	pKs 1	pKs 2	pKs 3	Solubility g/l (°C)
Glutamic acid	2.19[a]	4.25[a]	9.67[a]	7.0[b] (20)
Sebacic acid (C_{10})	4.40[a]	5.31[a]	–	1.0[b] (20)
Azelaic acid (C_9)	4.52–4.59[c]	5.36–5.56[c]	–	2.4[c] (15)
Adipic acid (C_6)	4.41–4.43[c]	~5.6[c]	–	14.4 (15)
Succinic acid (C_4)	~4.18[c]	5.36–5.63[c]	–	68.4[c] (20)
Lauric acid	~4.3[c]	–		0.023[c] (15)

[a] Experimentally determined.
[b] Merck index.
[c] Beilstein.

The solubilities of the used model drugs at 37°C are 995 g/l for pentoxifylline, 11.2 g/l for theophylline and 0.74 g/l for theobromine. Ethylcellulose, Eudragit RL-PO and the microcrystalline cellulose are practically insoluble.

3. Results and discussion

3.1. Carboxylic acids and glutamic acid as additives

3.1.1. pH-dependence of release

The addition of carboxylic acids or glutamic acid to PVA 100 000 leads to a late burst in the release profile in the case of sebacic acid, azelaic acid, adipic acid and glutamic acid (Fig. 2). Succinic acid und lauric acid do not show the desired effect. The release process was examined more closely in the case of glutamic acid as additive. Both the time and the extent of the burst can be influenced by variation of the added amount of glutamic acid. The correlation of the amount of glutamic acid added to PVA 100 000 as basis polymer with the mean dissolution times for 80% of drug release (MDT 80%) of the formulations shows a nearly linear decrease of the MDT 80%-values with increasing amounts of glutamic acid (Fig. 3).

To investigate the influence of the pH-values of the media on the release of the formulation with glutamic acid, release studies are performed at different pH-values (Fig. 4). Only

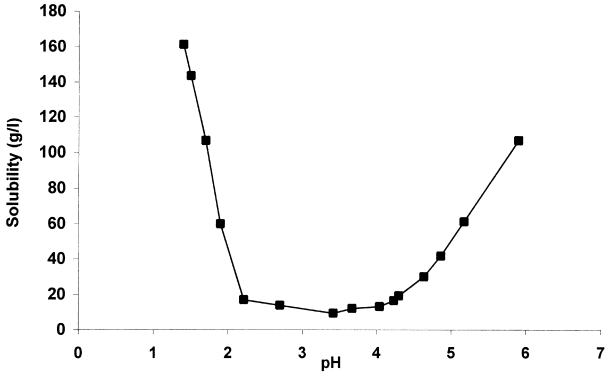

Fig. 1. pH-solubility profile of glutamic acid.

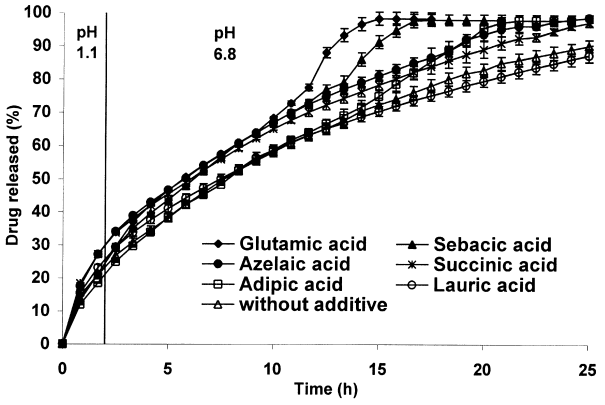

Fig. 2. Release of pentoxifylline 100 mg: PVA 100 000 500 mg, acids 200 mg; change of pH 1.1–6.8 after 2 h.

in a very acid environment (pH 1.1) the dissolution process occurs without a burst. At all higher pH-values, starting with pH 2.3, an acceleration after approximately 10 h is observed. No statistically significant differences are found between the individual release rates at pH-values between 2.3 and 7.8. The overlapping standard deviations are omitted in Fig. 5 for the purpose of a more clear presentation. Interestingly, the relatively high solubility of glutamic acid at pH 1.1 leads to a relatively fast diffusion controlled release with no burst until the end of release.

At pH-values between 2.3 and 4.5, large fractions of glutamic acid are present as zwitterion with low solubility. The release slows down and a burst occurs at about 10 h. Thus, not highly but sparingly soluble additives seem to induce the desired burst. This also explains the ineffectiveness of the highly soluble succinic acid. The sparingly soluble lauric acid is an exception, probably because of its hydrophobic and greasy character.

Surprisingly, in the case of pH-values higher then 4.5 in the dissolution media, the release pattern in presence of glutamic acid does not change, in spite of the good solubility of glutamic acid at pH-values above 4.5. Supposedly, there

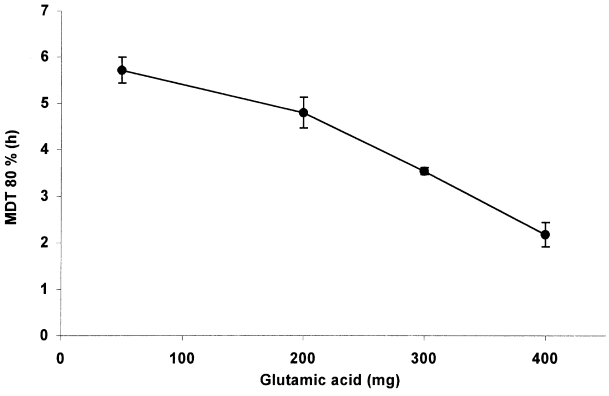

Fig. 3. Release of pentoxifylline 100 mg: PVA 100 000 700-x mg, glutamic acid x mg; change of pH 1.1–6.8 after 2 h: MDT 80% - values vs. added amount of glutamic acid.

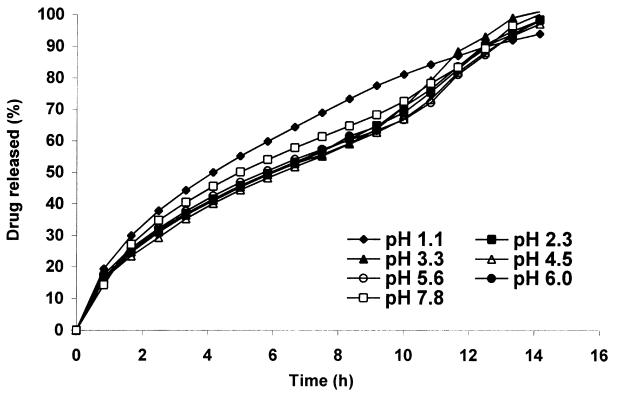

Fig. 4. Release of pentoxifylline 100 mg: PVA 100 000 500 mg, glutamic acid 200 mg; different pH-values of the dissolution medium.

is a pH-value in the interior of the swollen hydrocolloid dosage form different from that in the surrounding dissolution medium, due to the buffering effect of the incorporated glutamic acid. This interior pH determines the observed release rate. Such pH-dependent effects concerning the dissolution [13], respectively, the release of drugs from microcapsules [14] are already described in the literature.

To prove this hypothesis, pH color indicators are added to the tablet formulation. After the addition of such color indicators it becomes obvious that the pH-value within the tablet is dominated by the acid properties of the glutamic acid. The pH-value in the interior of the hydrocolloid dosage form never exceeds a value of 4.5, even if the surrounding medium has a pH of 7.8. Therefore, the acid milieu within the tablets determines the low solubility of glutamic acid. This explains the identical dissolution behaviour of pentoxifylline at all pH values higher than 2.3. As conclusion it may be stated: if pH-dependent soluble substances are used as release modifiers in hydrocolloid dosage form, the intrinsic pH-value of the tablet must be considered in addition to the pH-value of the dissolution medium.

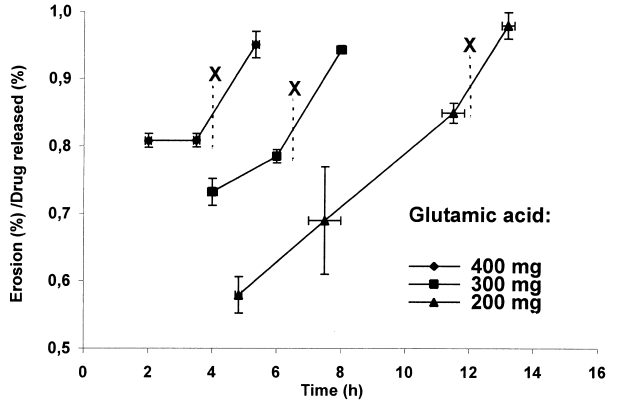

Fig. 5. Release of pentoxifylline 100 mg: PVA 100 000 700-x mg, glutamic acid x mg; quotient of erosion (%) and drug release (%) as a function of time; the occurrence of the release progression is marked with X on a dotted line. The symbols represent 30, 50 and 70% of release (additionally 90% with 200 mg glutamic acid) at pH 6.8.

3.1.2. Correlation of drug release with erosion

Under the release condition of pH 6.8, it is shown in Fig. 5 that increasing amounts of glutamic acid lead to a faster release and to a higher degree of erosion: The quotients erosion (%)/drug release (%) are increased at all times. Furthermore, the burst starts earlier and correlates with increasing erosion in the final phase of release, the quotient is near 1. The entire process runs predominantly erosion controlled, if the amount of glutamic acid in the formulation is raised to 400 mg (50%). Further increasing the amount of glutamic acid leads to an early disintegration of the tablet. On the other hand, no burst is achieved with an amount of glutamic acid less than 50 mg, the dissolution process is then predominantly diffusion controlled.

3.2. Addition of drugs with different solubilities

To clarify the mechanism of the burst in the release profile, drugs with different solubilities are used. Erosion control of the release process for poorly soluble drugs from hydrocolloid carriers was first mentioned by Ford [15]. Lindner [16], described increasing erosion control with decreasing solubility of the incorporated drug. The term solubility has to be considered here in connection with the amount of water available in the swollen tablet for the dissolution process. In this study, the incorporated amount of 300 mg theophylline would require about 27 ml of water for complete dissolution. The tablet volume, however, is only approximately 0.6 ml. Even after swelling, the dissolution of theophylline is certainly not complete. Three hundred milligrams of pentoxifylline would need only about 0.3 ml of water, which seems possible. Theobromine, practically insoluble, will nearly not dissolve within the swollen tablet.

Fig. 6 shows that the release process proceeds almost exclusively diffusion controlled and no burst occurs, if the readily soluble pentoxifylline is used. In the case of theophylline, the release is first slowed down compared to pentoxifylline. However, a burst is observed after 18 h. A further deceleration at the beginning of the release is

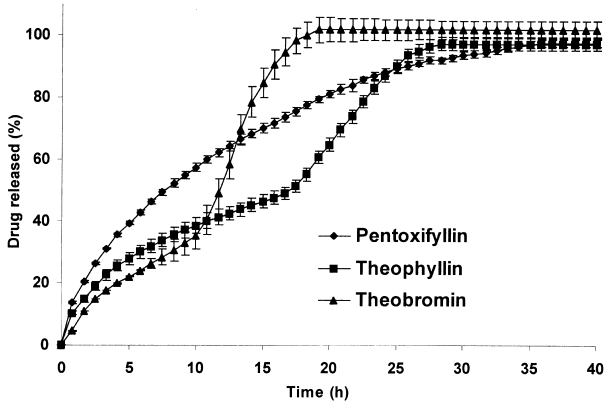

Fig. 6. Release of drugs with different solubilities: PVA 100 000 500 mg, drug 300 mg at pH 6.8.

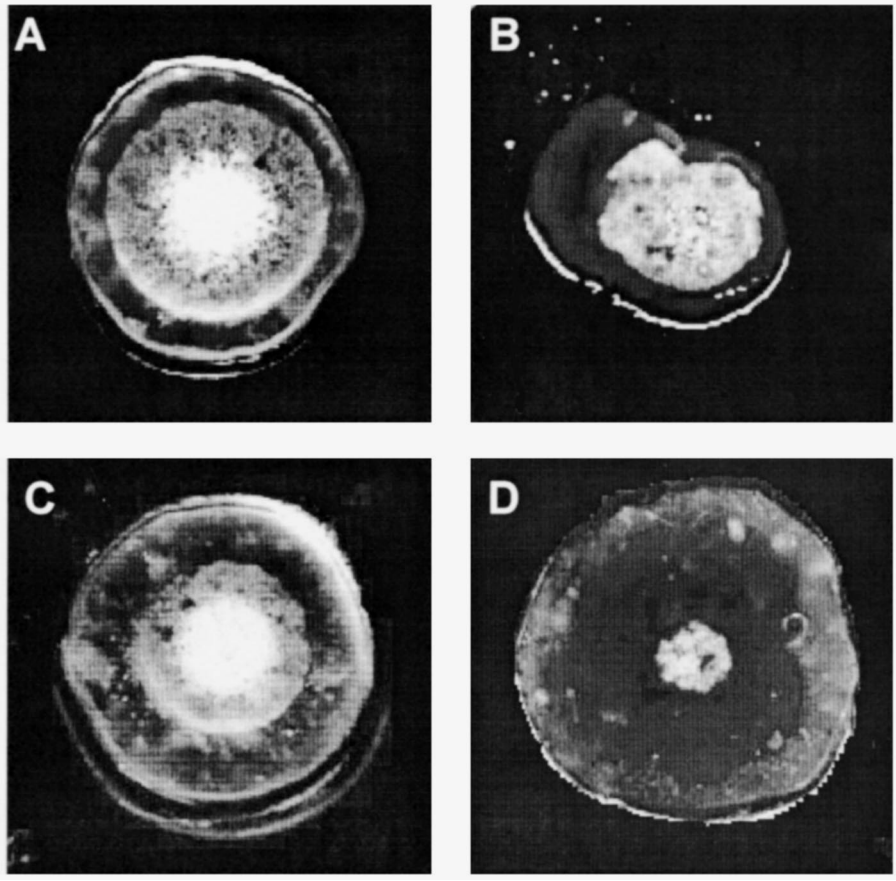

Fig. 7. Images of PVA 100 000 tablets containing additionally 2 mg of methylene blue during dissolution at pH 6.8; tablets fixed in the perspex mount: (A) PVA 100 000 500 mg, theophylline 300 mg; after 28 h, (B) PVA 100 000 500 mg, theophylline 300 mg; after 70 h, (C) PVA 100 000 500 mg, pentoxifylline 300 mg; after 28 h, (D) PVA 100 000 500 mg, pentoxifylline 300 mg; after 70 h.

observed after incorporating theobromine in the tablet, but also an earlier and more marked burst.

Release studies with the perspex mounts and imaging the tablets show erosion of the surrounding gel layer. In the case of theobromine and theophylline, the drugs induce a burst. Three layers become detectable by methylene blue dyeing: A dry core, a region which is already partially swollen, and a transparent, completely swollen outer gel layer (Fig. 7).

Fig. 9 represents the changes of the tablet structure during the complete release with theophylline as drug. It should be noted that the dissolution runs over a longer period of time as in the official paddle apparatus, since the dissolution medium can only reach the body surface of the tablet in the mount. The increased drug release after about 50 h (Fig. 8) has two reasons.

1. At the time point at which the dry core disappears, the drug still incorporated in the gel layer is released by accelerated erosion and/or disintegration.
2. The reduction of the gel layer shortens the diffusion way for the remaining drug in the tablet.

With the readily soluble pentoxifylline, no erosion of the gel layer could be observed.

3.3. Addition of insoluble excipients

According to the previous results it seems likely that a burst in the release profile can be achieved by incorporation of sparingly soluble substances in hydrocolloid tablets. In order to test this hypothesis, insoluble excipients are added to PVA 100 000 as basis polymer. The results are represented in Fig. 9.

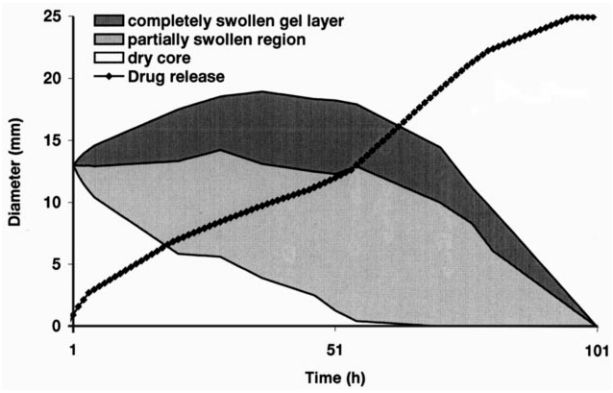

Fig. 8. Release of theophylline 300 mg and change of the tablet structure: PVA 100 000 500 mg; tablet fixed in the perspex mount; pH 6.8.

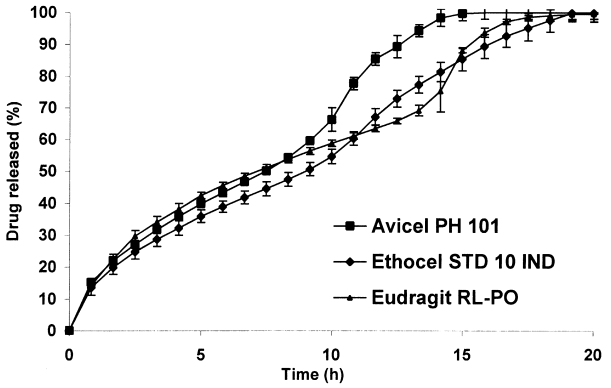

Fig. 9. Release of theobromine 20 mg: PVA 100 000 500 mg, insoluble additives 280 mg.

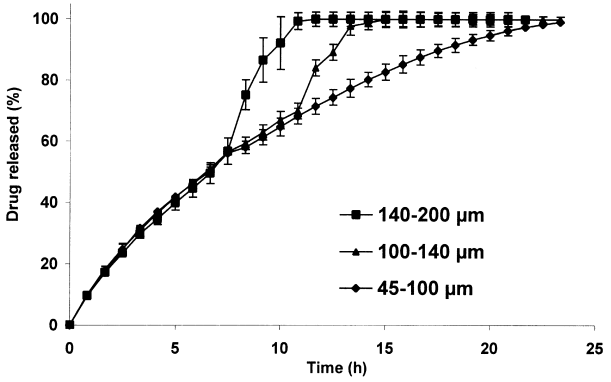

Fig. 10. Release of theobromine 20 mg: PVA 100 000 500 mg, Eudragit RL-PO 280 mg.

With microcrystalline cellulose (Avicel PH 101) as additive to PVA 100 000 a burst is observed after approximately 50% of release. Ethylcellulose (Ethocel STD 10 IND) shows a similar but less pronounced effect. With Eudragit RL-PO as insoluble addition a burst is observed after approximately 70% of drug release. The onset times are different but well reproducible for the three additives: microcrystalline cellulose 8.61 ± 0.50 h, ethylcellulose 10.83 ± 0.68 h, Eudragit-RL-PO 13.72 ± 0.52 h. The three insoluble additions induce a burst in the release profile not only for sparingly soluble drugs like theobromine but also for slightly and readily soluble drugs like theophylline and theobromine. The burst is nearly independent of the particle size of the added excipients, but depends on the particle size of the used basic polymer (Fig. 10). Only above the critical particle size of 45–100 μm a burst in the release profile is observed. Up to a theobromine release of about 50% the release runs with the same rate for the three investigated particle sizes of the basic polymer and Eudragit RL-PO as additive. Above 50% of release increasing particle size leads to an earlier and more pronounced burst.

3.4. Investigations of other polymers

So far the release behaviour with a burst in the final phase described above is only observed with PVA 100 000 as hydrocolloid basis. Other types of polymers used in hydrocolloid tablets such as methylhydroxy propylcelluloses, methylhydroxy ethylcelluloses or hydroxypropyl celluloses do not exhibit a burst. They either show fast disintegration of the hydrocolloid dosage form or the surrounding gel layer is sufficiently stable and prevents a burst until the end of release.

Therefore, different polyvinyl alcohols are examined in further studies to find other polyvinyl alcohols with a burst in their release profiles. The results of these studies are summarized in Table 2. Both the viscosity number and the degree of the hydrolysis of the appropriate polyvinyl alcohol influence the occurrence of a burst. It is evident, that the viscosity number and the degree of hydrolysis have to be in a specific ratio to achieve a burst in the release profile. A high degree of hydrolysis leads to decreasing solubility of the polyvinyl alcohol due to an increasing cristallinity [17]. If, in addition to low solubility, the viscosity and subse-

Table 2
Dissolution studies for other polyvinyl alcohols at pH 6.8: PVA 500 mg, Eudragit RL-PO 280 mg, theobromin 20 mg

No.	Type	Viscosity (4% sol.) (mPas)	Degree of hydrolysis (mol%)	*P*-value (mPas/mol%)	Progression (yes/no)	
1	Polyviol WX 28/20	28 ± 2[a]	97.5–99.5[a]	18.67	No	Diffusion control
2	Mowiol 20/98	20[a]	98[a]	10	No	Diffusion control
3	Mowiol 10/98	10[a]	98[a]	5	No	Diffusion control
4	PVA 100 000	35–45[a]	86–89[a]	3.2	Yes	Progression after 11 h
5	Polyviol M 05/20	5 ± 0.5[a]	97.5–99[a]	2.86	Yes	Progression after 17 h
6	Polyviol W 25/100	25 ± 1.5[a]	90–93[a]	2.94	Yes	Progression after 5 h
7	Polyviol W 25/140	25 ± 1.5[a]	86–89[a]	2	Yes	Progression after 11 h
8	Polyviol W 25/190	25 ± 1.5[a]	81–84[a]	1.43	No	Rapid dissolution
9	Polyviol M 13/140	13 ± 1[a]	86–89[a]	1.04	No	Rapid dissolution
10	Polyviol W 45/450	45 ± 5[a]	42–50[a]	0.80	No	Rapid disintegration
11	Polyviol M 05/140	4.5 ± 0.5[a]	86–89[a]	0.36	No	Rapid disintegration

[a] Manufacturer's specifications.

quently the stability of the gel layer is relatively high [18], no burst occurs. This could be observed in the case of Polyviol WX 28/20 for example. On the other hand, with a low viscosity number and a low degree of hydrolysis the stability of the gel layer is not sufficient enough, the system is subjected to a rapid dissolution or disintegration. An example is Polyviol M05/140. Only if relatively low gel viscosity is compensated by low solubility or if a gel with a high tendency to dissolve shows a high viscosity, a burst occurs. This is the case with PVA 100 000, Polyviol M05/20, Polyviol W25/100 and Polyviol W25/10 (Table 2).

To allow a prediction whether a polyvinyl alcohol exhibits a burst in the release profile or not, the characteristical number P is introduced (Eq. 2):

$$P = \eta/(100 - H) \quad (2)$$

where η is the viscosity of a solution containing 4% of the polyvinyl alcohol and H is the degree of hydrolysis in mol%.

Table 2 indicates the individual P-values of the examined polyvinyl alcohols. Polyvinyl alcohols with high P-values show diffusion controlled release with no detectable burst. Polyvinyl alcohols with low values tend to erosion controlled release. Only polyvinyl alcohols with P-values around 2–3.2 show an acceleration of release.

Thus, it can be assumed that with the help of the P-values it is possible to predict the suitability of a polyvinyl alcohol for the creation of an oral controlled release system with a burst in the release profile.

4. Conclusion

From the results of this study it can be concluded that polyvinyl alcohols with a special ratio of viscosity number to degree of hydrolysis are suitable hydrocolloid carriers to obtain dissolution profiles with a burst. An accelerated release occurs only with the addition of sparingly soluble compounds to the embedding.

Acknowledgements

We would like to thank Roche Diagnostics, Mannheim, for their financial support.

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